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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,623	06/20/2003	Uri H. Saragovi	OGIL-002 US	7195

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,623	SARAGOVI ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-35,38 and 39* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/21/2006 has been entered.

Claims 1-29, 31-35 and 38-39 are pending.

Claims 1-29 and 31-34 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 35 and 38-39 are currently under consideration.

Information Disclosure Statement

The information disclosure statement filed on June 21, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the

instant case, the claims are inclusive of a genus of compounds of the formula W-Z-X, wherein X is doxorubicin or paclitaxel, Z is a breakable linker and W is a targeting moiety, wherein the targeting moiety is a genus of antibodies that selectively bind to a polypeptide expressed on the surface of a tumor cell. However, the written description in this case only sets forth a compound of formula W-Z-X, wherein X is doxorubicin or paclitaxel, Z is a breakable linker and W is a monoclonal antibody selected from the group consisting of a-IR3; 5C3 and MC192.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 4, line 31 to page 5, line 10) that the compounds of the invention include, but are not limited to, compounds represented by the formula W-Z-X, wherein X is a therapeutic agent such as a chemotherapeutic agent or an antiviral agent, Z is a cleavable linker which is breakable by pH modification, reduction or enzymatic hydrolysis and W is a molecule which is adapted to selectively bind the target cell directly or indirectly such as an antibody. Specifically, the specification teaches (page 5, lines 17-22) that chemotherapeutic include not only include taxanes, but also any chemotherapeutic agent such as taxane derivatives, doxorubicin, or daunomycin. In addition, the specification teaches (page 6, lines 11-13) that antibodies of the preferred embodiment include monoclonal antibodies MC192, 5C3 or α-IR3. However, the written description (specification, page 10, lines 24-33 and page 24, line 16 to page 24, line 24) only reasonably conveys one species of a compound of formula W-Z-X, wherein X is doxorubicin, Z is a cleavable linker, and W is monoclonal antibody selected from the group consisting of a-IR3; 5C3 and MC192. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of

cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of conjugates that encompass the genus of compounds of formula W-Z-X that bypass p-glycoprotein-mediated resistance nor does it provide a description of structural features that are common to the compounds of formula W-Z-X. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of compounds which bypass p-glycoprotein mediated resistance is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of compounds, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a compound of formula W-Z-X, wherein X is doxorubicin or paclitaxel, Z is a cleavable linker, and W is a monoclonal antibody selected from the group consisting of a-IR3; 5C3 and MC192, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to this rejection, Applicants assert that the specification teaches how to make and use compounds of the invention in which doxorubicin and paclitaxel are the chemotherapeutic agents. Applicants further assert that, as the Examiner points out, the specification as filed provides a written description for compounds of the invention comprising monoclonal antibodies directed to p75 neutophin receptor (p75), neurotrophic tyrosine receptor kinase (TrKA) or insulin-like growth factor receptor, type 1 (IGF-1R) polypeptide. (Office Action at page 6, lines 10-12). For example, Applicants contend that the invention provides for monoclonal antibodies such as a-IR3; 5C3; and MC192, which are directed to these polypeptides. Applicants contend that they have demonstrated utility of the compounds of the invention which include monoclonal antibodies directed to p75 neutophin receptor (p75), neurotrophic tyrosine receptor kinase (TrKA) or insulin-like growth factor receptor, type 1 (IGF-1R) polypeptide, wherein these polypeptides are representative of a genus of polypeptides which share the biological characteristics of being expressed on the surface of tumor cells, including drug-resistant tumor cells. Thus, Applicants assert that one skilled in the art would recognize that other compounds of the invention which include monoclonal antibodies directed to polypeptides expressed on the surface of tumor cells, including drug resistant tumor cells would be useful in the method of claim 35.

These arguments have been carefully considered, but are not found persuasive.

With respect to Applicants assertion that the specification teaches one of skill in the art how to make and use the instant application, the Examiner agrees with Applicants assertion that one skilled in the art would know how to make and use the invention. However, the Examiner recognizes that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). In the instant case, the claims encompass a genus of molecules defined solely by its principal biological property, e.g., binds to a polypeptide expressed on a tumor cell, which is simply a wish to know the identity of any material with that biological property. Accordingly, there is insufficient written description encompassing an

"antibody that binds to a polypeptide present on a tumor cell" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed. Regarding Applicants assertion with respect to what the Examiner pointed in the prior office action, the Examiner recognizes that in the prior office action he stated "while the specification disclose a species of monoclonal antibodies specific for IGF-IR, p75 receptors and TrkA and appears to be silent on the structural features that are common to the genus of ligands. As such, the specification only reasonably conveys three species of targeting agents, wherein the targeting agents are antibodies to IGF-IR, p75 and TrkA." Therefore, it appears that Applicants misinterpreted the Examiners previous statement to include a genus of antibodies that bind to IGF-IR, p75 and TrkA, but clearly the Examiner's previous statement was directed to the disclosure of one species for each of the three genus which is insufficient to describe the genus as a whole. Therefore, only a compound of formula W-Z-X, wherein X is doxorubicin or paclitaxel, Z is a cleavable linker, and W is a monoclonal antibody selected from the group consisting of a-IR3; 5C3 and MC192, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear whether a cell line which produces an antibody having the exact chemical identity of α-IR3, 5C3 or MC192 is known or publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one or ordinary skill in the art could not be assured of the ability to practice the claimed invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 2D12.5. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See, 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an addition means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC) and 37 CFR 1.801-1.809 for further information concerning deposit practice.
In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Trail et al. (Clinical Cancer Research 1999; 5: 3632-3638, IDS) as evidenced by Willner et al. (Bioconjugate Chem. 1993; 4: 521-527) and Dietro et al. (Braz. J. Med. Biol. Res. 1999; 32; 925-939, *of record*).

Trail et al. teach a method of treating a patient with a tumor comprising tumor cells, including drug-resistant tumor cells, said method comprising administering an immunoconjugate referred to as BR96-Doxorubicin (beginning on page 3634, 2nd column, *Effect of Combined Therapy with BR96-Doxorubicin on Paclitaxel-resistant Human Colon Tumor Xenografts* and page 3636, Figure 3). With regard to Br96-doxorubicin, the reference teaches that BR96-doxorubicin immunoconjugates binds to a Le^y-related tumor associated antigen abundantly expressed on the majority of human carcinomas (page 3632, 2nd column, 1st full paragraph). Thus, while Trail et al. do not specifically teach the chemical structure of BR96-Trail as having a breakable linker which covalently links BR96 to doxorubicin and cleaves in the cells for releasing doxorubicin into said cells, the clamed limitation does not appear to result in a manipulative difference when compared to the prior art disclosure because as evidenced by Willner et al., conjugates comprising a hydrazone as the linker, such as in BR96-DOX, are internalized into the acidic environment of the lysosomes where DOX is released

from the acid-labile linker (page 521, 1st column, 1st paragraph and page 522, 1st column, 1st full paragraph). Moreover, while Trail et al. do not characterize the tumor cells as tumor cells including drug-resistant tumor cells mediated by the p-glycoprotein pump, the claimed limitation does not appear to result in a manipulative difference in the prior arts disclosure since resistance to chemotherapy in cancer cells is mainly mediated by overexpression of p-glycoprotein as evidenced by Dietro et al. (Braz. J. Med. Biol. Res. 1999; 32; 925-939).

Therefore, No claim is allowed.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Saragovi et al. (US 6,610,500, 1997), considered to be the closest prior art for a the monoclonal antibody 5C3, teach an agonistic anti-human TrkA mAb 5C3 which recognizes the NGF docking site, wherein the antibody may be used for the treatment, diagnosis or prevention of neurological diseases, neuromas and neoplastic tumor which express TrkA receptors. However, Saragovi et al. does not teach or suggest forming a conjugate comprising 5C3 and doxorubicin or paclitaxel for the treatment of tumors, including drug-resistant tumor cells mediated by p-glycoprotein pump. As such, claim 39 appears to be free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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